peptide (CTB) or an *E. coli* heat-labile enterotoxin B subunit (LTB) peptide in an unconjugated form.

REMARKS

This is in response to the Examiner's Final Office Action dated January 30, 2001. Claims 1-3 and 5-20 are pending in this application, with claims 21-26 withdrawn from consideration by the Examiner under 37 C.F.R. §1.142(b) as being drawn to a non-elected invention. Applicants express their appreciation for the withdrawal of the rejections of claims 1, 2 and 5-20 under 35 U.S.C., §112, 1st paragraph and claims 12, 13 and 14 under 35 U.S.C. 102(e).

Claims 1, 12, 15, 19 and 20 are amended to specify that the sustained immunological tolerance generated by the claimed methods are "specific" for the target antigen. Support for the amendment is found on page 8, line 7 of the Specification and several other locations. No new matter is added. This Amendment after Final is presented to more clearly define the present invention and to present the rejected claims in better form for consideration on appeal. The Examiner is respectfully requested to enter the amendments.

Reconsideration of the application is respectfully requested in view of the above amendments to the claims and the following remarks. For the Examiner's convenience and reference, Applicants' remarks are presented in the order in which the corresponding issues were raised in the Office Action.

Attached hereto is a marked-up version of the changes made of the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made**".

I. Rejection under 35 U.S.C. §103(a)

Claims 1-2 and 5-20 stand rejected under 35 U.S.C. §103(a) for obviousness over JP3109328 in view of Elson (Curr. Topics in Microbiol. 146, 29-33 (1989)).

The Examiner cites JP3109328 to "demonstrate that CTB, when administered with a substance which normally results in an immune response (graft rejection of bone marrow cells) abrogates the normal rejection." (Office Action of January 30, 2001, page 3, paragraph 3; emphasis added). Applicants respectfully traverse the Examiner's interpretation of this Japanese document.

The disclosure in JP3109328 concerns induction of tolerance towards a graft transplant by administering CTB alone. CTB is **not** administered "as an effective combination" with a substance which normally results in an immune response as specified in the claimed invention, but is specifically administered prior to or simultaneously with said substance. According to JP3109328, the mucosal binding agent (CTB) is administered **on or before** the administration of the antigen(s) to generally suppress the immune system from rejecting the graft. The CTB can even be administered by a separate route "preferably through a non-transintestinal route such as vein, peritoneal cavity or muscle." (JP3109328, Abstract). The suppression of the immune system by this method is not a specific one but the observed tolerance is of a general nature which results in abrogation of normal graft rejection.

General suppression of the immune system as disclosed in JP3109328 has its disadvantages. General suppression of the immune system postpones rejection of the bone marrow cells, however it also suppresses the immune system's ability to react with potentially disease-causing antigens. Similar disadvantage is observed in graft recipients receiving general immune suppressing drugs and in other patients with impaired immune systems.

By contrast, the present invention seeks to achieve a **specific** and **sustained** suppression of immune reactivity against selected target molecules and not a general, non-specific suppression of

the immune system. (Specification, page 2, lines 1-4). This is achieved in the claimed invention by "administering to a mucosal surface of the individual a composition comprising **an effective combination** of an inducing agent and a mucosal binding component selected from the group consisting of a cholera toxin B peptide (CTB) or an *E. coli* heat-labile enterotoxin B subunit (LTB) peptide in an unconjugated form." Specific tolerance in a sustainable form against a target antigen is induced by **prior** mucosal administration of the target antigen. Thus, future administrations of the target antigen are specifically tolerated according to the claimed methods of the invention. By contrast, according to JP3109328, a general tolerance is induced by prior administration of the CTB and not the target antigen.

As is generally known in the field of immunology, the mucosal immune system differs from the systemic immune system in that the response in the mucosa is more biased towards tolerance. (Specification page 2, line 10 to page 3, line 2). Applicants present for the Examiner's reference an article by Allan Mcl. Mowat (*Oral Tolerance and Regulation of Immunity to Dietary Antigens*. Handbook of Mucosal Immunology (Eds. Ogra, PL et al.), pp. 185-201 (Academic Press, 1994)) which states that specific immunological tolerance to an antigen is effected by **prior** oral administration of the antigen. (Mowat, pp. 185-186). This refers to the method of the claimed invention and is distinct from the method according to JP3109328.

T cells generated in a tolerance response according to the claimed invention are directed at the specific antigen and exhibit their immune suppressing effect only in those areas of the body where the specific antigen is presented. This enables specific suppression of the immune response in the affected areas only, e.g., in the bone marrow in case of transplants or, in the pancreas in case of type 1 diabetes. The present invention also demonstrates that even where a bystander antigen is used to elicit the specific tolerance of the target antigen, T cell suppression is elicited only at the specific

organs where the bystander antigen is presented. (Specification, page 18, lines 12-22 and Table 1). This is a clear advantage of the present invention over the general suppression of the immune system achieved in JP3109328.

In terms of tissue transplantations, the present invention specifies that "specific, sustained, immunological tolerance" to a target antigen is only achieved by administering the target inducing agent to the mucosal surface "as an effective combination" with the CTB. (Specification, page 7, lines 3-15). Thus, the inducing antigens (e.g., HLA antigens) present in the transplanted tissue and responsible for eliciting immunological rejection against the graft are to be administered **in combination with** the mucosal binding component to the mucosal surface **prior to** transplantation in order to induce specific tolerance of the transplant tissue. This is neither taught nor suggested by JP3109328 which teaches away by suggesting that the administration of the inhibitory agent (CTB) can occur prior to transplantation and can be preferably effected by separate administration through a "non-transintestinal route such as vein, peritoneal cavity or muscle." (JP3109328, Abstract).

Elson (Curr. Topics in Microbiol. 146, 29-33 (1989)) also does not disclose specific sustained immunological tolerance to a target antigen. Elson primarily concerns the field of adjuvants, especially the adjuvant properties of CT and CTB and oral **immunization**. Elson demonstrates the **stimulation** of antibody response towards an antigen which is orally presented along with CT and CTB. Elson addresses CT/CTB as an mucosal adjuvant but repeatedly specifies that "CT feeding **does not induce oral tolerance**" (page 30, lines 4 and 30). The enclosed Mowat article on page 196 (col. 2, last paragraph) confirms the use suggested by Elson of CTB as a mucosal adjuvant to stimulate antibody response for an oral **vaccine**. Thus Elson also teaches away from the present invention which, in contrast, specifies the specific **tolerance** of a target antigen by **suppression** of the immune response to said antigen.

Applicants present for the Examiner's reference an article by Elson and Ealding (J. of Immunology, 132(6):2736-2741 (1984)) which states that the increased immunization caused by mucosal administration of CT is different from oral tolerance which may be caused by exposure to intestinal antigens and which is generally believed to be effected by the generation of antigen-specific suppressor T cells (Elson and Ealding, page 2740, col. 1, line 35 to col. 2, line 4). Neither Elson nor Elson and Ealding teach or suggest any induction of "specific sustained immunological tolerance" by administering a mixture of CTB and target antigen as specified in amended, independent claims 1, 12, 15, 19 and 20.

The Examiner also mentions that Elson states that "intestinal administration of mixtures of CTB plus antigen would not stimulate antibody response to the latter in the intestine or in the serum. (page 31, first paragraph and second paragraph)." (Office Action of Jan. 30, 2002, page 3). Applicants respectfully traverse the Examiner's conclusion that this is equivalent to an induced mucosal tolerance. The "absence of stimulation," or the lack of adjuvant properties of CTB when mixed with an antigen is **not the same** as an "induction of specific tolerance" which will be manifest in future administrations of the target antigen even when presented without CTB. Applicants enclose a published article by Howard L. Weiner (*Oral Tolerance for the Treatment of Autoimmune Diseases*, Ann. Rev. Med. 48:3410351 (1997)) which describes the mechanism of oral tolerance and states that suppression is an active process **unrelated** to the lack of stimulation of an antigen response. (Weiner, pp. 342-343).

In order to further illustrate the difference, Applicants present for the Examiner's reference an article by McKenzie and Halsey (J. of Immunology, 153(4):1818-1824 (1984)) which demonstrates that a mixture of CTB and antigen (horse radish peroxidase) elicits an antibody response similar to that seen against the antigen alone but less than that against a conjugate between

CTB and the antigen. (Tables I and II, page 1822). Thus, the mention by Elson (page 31, first paragraph) of intestinal administration of CTB and antigen mixtures being ineffective in stimulating antibody responses to the antigen, when viewed in light of the observed adjuvant effect reported by McKenzie and Halsey when the CTB and antigen are conjugated, can only be construed as a statement by Elson that there is no adjuvant effect (stimulation of the immune response) when the antigen and CTB are presented in an unconjugated form. There is no suggestion in McKenzie and Halsey of any induction of oral tolerance. On the contrary, CT and CTB are mentioned as exceptions to cases of induced systemic oral tolerance. (page 1818, col. 2, lines 14-22).

Elson does not teach or suggest any reason why one skilled in the art would expect that administering CTB as a mixture with an antigen to a mucosal surface would engender a specific immunotolerance to the antigen. The abstract of JP3109328 specifies a general immunosuppression method for use during transplantation of bone marrow cells by separate administration of CTB. Elson and JP3109328, by themselves or in combination, do not teach or suggest potentiation of "specific sustained immunological tolerance" in an individual to a target antigen by coadministration of CTB and target antigen by the mucosal route as specified in amended, independent claims 1, 12, 15, 19 and 20. Claims 2, 3, 5-11, 13, 14 and 16-18 depend from these independent claims. Since the combination of Elson and JP3109328 do not teach or suggest all the elements of the claimed invention, Applicants respectfully request that the rejection of these claims under 35 U.S.C. §103(a), be withdrawn.

In light of the arguments set forth above, Applicants earnestly believe that they are entitled to a letters patent and respectfully request the Examiner to expedite prosecution of this patent application to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 273802002200. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

1. (Twice Amended) A method of inducing specific sustained immunological tolerance in an individual to a target antigen, comprising administering to a mucosal surface of the individual a composition comprising an effective combination of an inducing agent and a mucosal binding component selected from the group consisting of a cholera toxin B peptide (CTB) or an *E. coli* heat-labile enterotoxin B subunit (LTB) peptide in an unconjugated form.

12. (Thrice Amended) A method of inducing specific sustained immunological tolerance in an individual to an allergen or a mucosal antigen, comprising administering to a mucosal surface of the individual a composition comprising an effective amount of a mucosal binding component selected from the group consisting of a cholera toxin B peptide (CTB) or an *E. coli* heat-labile enterotoxin B subunit (LTB) peptide in an unconjugated form.

15. (Amended) A method for treating an autoimmune condition in an individual, comprising inducing specific sustained immunological tolerance according to the method of claim 1.

19. (Twice Amended) A method of decreasing the risk of rejection in a recipient of a tissue graft transplanted from a donor, comprising inducing specific sustained immunological tolerance in the recipient to cells of the donor according to the method of claim 1 by administering to a mucosal surface of the recipient a composition comprising an effective combination of an inducing antigen and a mucosal binding component selected from the group consisting of a cholera toxin B peptide (CTB) or an *E. coli* heat-labile enterotoxin B subunit (LTB) peptide in an unconjugated form.

20. (Twice Amended) A method of decreasing the risk of graft-versus-host disease in a recipient from a tissue graft transplanted from a donor, comprising inducing specific sustained immunological tolerance in the donor to cells of the recipient according to the method of claim 1 by administering to a mucosal surface of the donor a composition comprising an effective combination of an inducing antigen and a mucosal binding component selected from the group consisting of a cholera toxin B peptide (CTB) or an *E. coli* heat-labile enterotoxin B subunit (LTB) peptide in an unconjugated form.